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| 10/092,934 | 03/08/2002 | Paul Averback | 018792-0199 | 7362 |

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| EXAMINER | |
|---|---|
| SANG, HONG | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/092,934 | AVERBACK, PAUL | |
| | Examiner | Art Unit | |
| | Hong Sang | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *8,10-16,30,32-38 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,17-29,31 and 39-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/18/02 & 1/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

**RE: Averback**

1. Applicant's election with traverse of Group III (claims 5-7 and 27-29) and species election of SEQ ID NO. 1, a fragment thereof, a homolog thereof, a variant thereof, or an enantiomer thereof in the reply filed on 8/23/05 is acknowledged. The traversal is on the ground(s) that examining all the groups together is not unduly excessive. Upon further consideration, Groups I, II and VII are rejoined with Group III and are under examination. However, other restrictions are still maintained for the reasons below.

Groups I-III, and VII are drawn to a method of treating benign tumor, malignant tumor, hyperplasia, hypertrophy, overgrowth of a tissue, malformation of a tissue, which are patentably distinct from the inventions of Group IV-VI, VIII-XXXI, drawn to a method of treating other conditions including infected tissues (virally, bacterially, parasititically), cosmetic modification, vascular disease, hemorrhoids, varicose veins, inflammatory disease, autoimmune disease, metabolic disease, hereditaryl/genetic disease, traumatic disease, physical injury, nutritional deficiency, amyloid disease, fibrotic disease, storage disease, congenital disease, enzyme deficiency disease, poisoning disease, intoxication, environmental disease, radiation disease, endocrine disease, degenerative disease. As indicated in the office action filed on 6/23/05, the invention from each group is patentably distinct from others because each group is drawn to a method of treating a pathologically and/or etiologically distinct condition that has a different criteria for success. Moreover each method requires different searches and such a search is

not co-extensive. Because of these reasons, the requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-3, 17-25, and 39-45 are linking claims. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP j 804.01.

3. The information disclosure statements (IDS) filed on 6/18/2002 and 1/15/2003 have been considered. Signed copies are attached hereto.

4. The preliminary amendment filed on 5/26/2004 is acknowledged.

5. Claims 1-46 are currently pending. Claims 8, 10-16, 30, 32-38 and 46 are withdrawn from further consideration as being drawn to nonelected inventions.

6. Claims 1-7, 9, 17-29, 31 and 39-45 are under examination.

***Claim Objections***

7. Claim 23 is objected to because it recites "SEQ ID NO 1" for AD7C-NTP. In the preliminary amendment filed on 5/26/2004, Figure 1 is amended wherein the SEQ ID NO: 1 is now the nucleotide sequence of AD7C-NTP and SEQ ID NO: 10 is now the amino acid sequence of AD7C-NTP. Claim 23 depends upon claim 1 and claims a method of treating a condition using a neural thread protein (NTP). However, claim 23 still recites SEQ ID NO: 1 for AD7C-NTP protein, appropriate correction is required.

***Specification***

8. The first line of the specification should be updated if applicant desires priority under 35 U.S.C. 1 19(e), 120, 121 and 3654c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application (s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No.___" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date 6f the parent application.

For additional information, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, 2nd paragraph*

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 22 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 44 recite "the NTP is part of a single new cloned recombinant molecule consisting of NTP and a molecule". What is "PART" of a molecule? Is it an amino acid and what is this amino acid? Also what is "NEW Cloned" molecule? Is it a new NTP and what makes "NTP" a "NTP" molecule?

### *Claim Rejections - 35 USC § 112, 1st paragraph*

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-7, 9, 17-29, 31 and 39-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a benign tumor, a malignant tumor, hyperplasia, hypertrophy, overgrowth of a tissue and malformation of a tissue in a patient requiring removal or destruction of cells comprising

locally administering (e.g. topically, intratumorally) to a mammal in need a therapeutically effective amount of the neural thread protein consisting of SEQ ID NO. 10, does not reasonably provide enablement for a method of treating any and all conditions in a patient requiring removal or destruction of cells comprising systemically administering (e.g. intravenously, intra-arterially, intraperitoneally) to a mammal in need a therapeutically effective amount of any and all neural thread protein (NTP) as well as fragments, variant, derivative, homolog, reverse-D peptide, and enantiomers of NTP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

*The nature of the invention*

Claims 1-7, 9, 17-29, 31 and 39-45 are drawn to a method of treating a condition in a patient requiring removal or destruction of cells comprising administering to a mammal in need a therapeutically effective amount of a neural thread protein (NTP) as well as fragments, variant, derivative, homolog, reverse-D peptide, and enantiomers of

NTP. Claims are further limited wherein said NTP is administered by a method selected from the group consisting of orally, subcutaneously, intradermally, intravenously, intramuscularly, intrathecally, intraperitoneally, intracerebrally (intraparenchymally), intracerebroventricularly, intraocularly, intra-arterially, intranasally, intratumorally, intralesionally, topically, and transdermally.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

*The breadth of the claims*

Claims 1-7, 9, 17-29, 31 and 39-45 are drawn to a method of treating a condition in a patient requiring removal or destruction of cells comprising administering to a mammal in need a therapeutically effective amount of a neural thread protein (NTP) as well as fragments, variant, derivative, homolog, reverse-D peptide, and enantiomers of NTP. Claims are further limited wherein said NTP is administered by a method selected from the group consisting of orally, subcutaneously, intradermally, intravenously, intramuscularly, intrathecally, intraperitoneally, intracerebrally (intraparenchymally), intracerebroventricularly, intraocularly, intra-arterially, intranasally, intratumorally, intralesionally, topically, and transdermally.

The condition to be treated encompasses any and all conditions including normal and diseased conditions that are caused by any pathogens, genetic mutations, injuries,

etc. The method encompasses *in vivo* treatment by administering to a patient a NTP either systematically or locally. A neural thread protein NTP encompasses any and all NTPs including SEQ ID NO 2-10, neuronal thread proteins, pancreatic thread proteins, any and all proteins which share homology or function similarities with neuronal thread proteins either known in the art or yet to be discovered, any fragments, homologs, variants, derivatives, peptide mimetics, reverse-d peptides, and enantiomers thereof.

*Quantity of experimentation*

The quantity of experimentation in this area is extremely large since it would require significant study to determine which of the NTPs or their fragments, homologs, variants, derivatives, peptide mimetics, reverse-d peptides, and enantiomers in fact are capable of treating any and all conditions, not only tumor, hyperplasia, hypertrophy, overgrowth of a tissue or malformation of a tissue. Moreover, there is significant variability in the structure and effects of the different NTPs and their fragments, homologs, variants, derivatives, peptide mimetics, reverse-d peptides, and enantiomers. The identification and characterization of each of these NTPs and their fragments, homologs, variants, derivatives, peptide mimetics, reverse-d peptides, and enantiomers would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

*The unpredictability of the art and the state of the prior art*

The art only teaches a method of treating a benign or malignant tumor in a

mammal comprising local administration of a therapeutically effective amount of a NTP-peptide selected from the group consisting of SEQ ID Nos: 23, 24, 25, 26, 28, 29, and 52 (see US Patent No. 6,924,266 B2, claims 4-7). The instant specification shows that acute necrosis of tissue (both normal tissue and tumor) can be induced by administration of AD7-NTP (SEQ ID NO. 10) at the sites of injection (see pages 45-46, Examples 2 and 3). Therefore, the cytotoxic and necrotic effect of AD7C-NTP (SEQ ID NO. 10) is not cell selective or site selective, AD7C-NTP (SEQ ID NO. 10) is toxic to any type of cells that are in contact with it at the dose used in the specification.

Neither the art nor the instant specification teach a method of treating any and all conditions in a patient requiring removal or destruction of cells comprising systemically administering to a mammal in need a therapeutically effective amount of any and all neural thread protein including AD7C-NTP (SEQ ID NO. 10), and NTP selected from the group consisting of SEQ ID Nos: 23, 24, 25, 26, 28, 29, and 52 (see US Patent No. 6,924,266 B2, claims 4-7).

Neither the art nor the instant specification teach a method of treating any other conditions other than tumor, hyperplasia, hypertrophy, overgrowth of tissue and malformation of tissue in a patient requiring removal or destruction of cells comprising administering to a mammal in need a therapeutically effective amount of any and all neural thread protein including AD7C-NTP (SEQ ID NO. 10) and NTP selected from the group consisting of SEQ ID Nos: 23, 24, 25, 26, 28, 29, and 52 (see US Patent No. 6,924,266 B2, claims 4-7).

Working examples

The specification teaches an *in vitro* method of treating glioma and neuroblastoma cells by AD7C-NTP (SEQ ID NO. 10), where significant cytotoxic effects are observed at 24 hrs and at 96 hours after treatment (see page 43, Example 1). The specification teaches a method of administering AD7C-NTP by direct injection to the skin of normal rats, wherein the necrosis is observed in muscle tissue, subcutaneous connective tissue and dermis at the sites where the AD7C-NTP (SEQ ID NO: 10) was injected (see page 45, Example 2). The specification further teaches a method of treating different human and non-human origin tumors by directly infiltrating the tumor with AD7C-NTP (SEQ ID NO: 10), wherein a significant necrosis of tumor cells after AD7C-NTP infiltration is observed (see page 46, Example 3). However, aside from these data, no working example is provided for a method of treating any other conditions by any other NTPs. No evidence is provided to one of skill in the art to indicate that NTPs including ACD7C-NTP (SEQ ID NO: 10) can be administered systemically for example intra-arterially or intravenously without affecting normal cells.

*Guidance in the specification*

The specification fails to teach how to use any NTPs other than AD7C-NTP (SEQ ID NO 10), to treat any conditions. The specification does not provide guidance on how to administer any NTPs including AD7C-NTP (SEQ ID NO. 10) systemically, e.g. intra-arterially or intravenously without harming normal cells. While specification suggests using a conjugate of NTPs, linked to a protein or other molecule, for *in vivo* delivery, the

specification fails to teach how to make such conjugates that is tumor- or site specific i.e. the activity of NTPs is shut down or inhibited during delivery and turned on only at required sites. As such, it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

*Level of skill in the art*

The level of skill in the art is high.

*Conclusion*

Thus given the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the *in vivo* use and the limited teachings in the art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 112, 1st paragraph***

13. Claims 17-19, 21, 22, 39-42 and 44-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

*The nature of the invention*

Claims 17-19, 21, 22, 39-42, and 44-45 are drawn to a method of claim 1, wherein the NTP is conjugated, linked, or bound to a molecule selected from the group consisting of an antibody, antibody fragment, and an antibody-like-binding molecule, wherein said molecule has a higher affinity for binding to a tumor or other target than binding to other cells, a method of claim 1 wherein NTP is conjugated, linked, or bound to a protein or other molecule, wherein the composition is cleaved at or near the site(s) of the tumor or other unwanted cells by a tumor- or site-specific enzyme or protease or by an antibody conjugate that targets tumor or other unwanted cells and so releases the NTP, a method of claim 1, wherein NTP is conjugated, linked, or bound to a protein or other molecule, wherein the composition releases the NTP upon exposure of the tissue to be treated to light, other forms of electro-magnetic radiation, and a method of claim 1, wherein the NTP is employed in combination with dendrimers, fullerenes and other synthetic molecules, polymers and macromolecules wherein the NTP is conjugated with, attached, to or enclosed in the molecule, polymer or macromolecule, either by

itself or in conjunction with a molecule with a higher affinity for binding to a tumor or other target than binding to other cells.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

*The breadth of the claims*

Claims 17-19, 21, 22, 39-42, and 44-45 are drawn to a method of claim, wherein NTP is conjugated, linked, or bound to a molecule selected from the group consisting of an antibody, antibody fragment, and an antibody-like-binding molecule, wherein said molecule has a higher affinity for binding to a tumor or other target than binding to other cells, a method of claim 1 wherein NTP is conjugated, linked, or bound to a protein or other molecule, wherein the composition is cleaved at or near the site(s) of the tumor or other unwanted cells by a tumor- or site-specific enzyme or protease or by an antibody conjugate that targets tumor or other unwanted cells and so releases the NTP, a method of claim 1, wherein NTP is conjugated, linked, or bound to a protein or other molecule, wherein the composition releases the NTP upon exposure of the tissue to be treated to light, other forms of electro-magnetic radiation, a method of claim 1, wherein the NTP is employed in combination with dendrimers, fullerenes and other synthetic molecules, polymers and macromolecules wherein the NTP is conjugated with, attached, to or enclosed in the molecule, polymer or macromolecule, either by itself or in

conjugation with a molecule with a higher affinity for binding to a tumor or other target than binding to other cells.

A neural thread protein NTP encompasses any and all NTPs including SEQ ID NO 2-10, neuronal thread proteins, pancreatic thread proteins, any and all proteins which share homology or function similarities with neuronal thread proteins either known in the art or yet to be discovered, any fragments, homologs, variants, derivatives, peptide mimetics, reverse-d peptides, and enantiomers thereof. The NTP conjugate encompasses any NTP conjugated, linked, or bound to any and all molecules including protein, antibody, antibody fragments, antibody-like-binding molecule, dendrimers, fullerenes, other synthetic molecules, polymers, macromolecules, nucleic acids etc. The method encompasses *in vivo* treatment by administering to a patient a NTP conjugate either systematically or locally. The condition to be treated encompasses any and all conditions including normal and diseased conditions that are caused by any pathogens or genetic mutations, injuries, etc.

*Quantity of experimentation*

The quantity of experimentation in this area is extremely large since it would require significant study to determine which of the NTP conjugates in fact are capable of treating any and all conditions, not only tumor, hyperplasia, hypertrophy, overgrowth of a tissue and malformation of a tissue. There is significant variability in the structure and effects of the different NTPs and different molecules to which a NTP is linked, conjugated, or bound. The identification and characterization of each of these NTPs

and each of the molecules to which NTPs is linked, conjugated, or bound would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

*The unpredictability of the art and the state of the prior art*

The art only teaches a method of treating a benign or malignant tumor in a mammal comprising local administration of a therapeutically effective amount of a NTP-peptide selected from the group consisting of SEQ ID Nos: 23, 24, 25, 26, 28, 29, and 52 (see US Patent No. 6,924,266 B2, claims 4-7). The instant specification shows that acute necrosis of tissue (both normal tissue and tumor) can be induced by administration of AD7-NTP (SEQ ID NO. 10) at the sites of injection (see pages 45-46, Examples 2 and 3). Therefore, the cytotoxic and necrotic effect of AD7C-NTP (SEQ ID NO. 10) is not cell selective or site selective, AD7C-NTP (SEQ ID NO. 10) is toxic to any type of cells that are in contact with it at the dose used in the specification.

Neither the art nor the instant specification teach a method of treating any and all conditions in a patient requiring removal or destruction of cells comprising systemically administering to a mammal in need a therapeutically effective amount of any and all neural thread protein including AD7C-NTP (SEQ ID NO. 10), and NTP selected from the group consisting of SEQ ID Nos: 23, 24, 25, 26, 28, 29, and 52 (see US Patent No. 6,924,266 B2, claims 4-7).

Neither the art nor the instant specification teach a method of treating any other conditions other than tumor, hyperplasia, hypertrophy, overgrowth of tissue and

malformation of tissue in a patient requiring removal or destruction of cells comprising administering to a mammal in need a therapeutically effective amount of any and all neural thread protein including AD7C-NTP (SEQ ID NO. 10) and NTP selected from the group consisting of SEQ ID Nos: 23, 24, 25, 26, 28, 29, and 52 (see US Patent No. 6,924,266 B2, claims 4-7).

Moreover, neither the art nor the instant specification teach how to make any and all conjugates of a NTP, linked, conjugated, or bound to any and all molecules, especially how to make a conjugate where NTP is conjugated with, attached, to or enclosed in the molecule, polymer or macromolecule and how to use all these conjugates to treat any and all condition in a patient (including tumor, hyperplasia, hypertrophy, overgrowth of a tissue, malformation of a tissue) requiring removal or destruction of cells.

The claims recites "the composition is cleaved at or near the site(s) of the tumor or other unwanted cells by a tumor- or site-specific enzyme or protease or by an antibody conjugate that targets tumor or other unwanted cells and so releases the NTP, or the composition releases the NTP upon exposure of the tissue to be treated to light, other forms of electro-magnetic radiation. However, neither the art nor specification teaches how to make such compositions which are capable of traveling to the sites of the tumor or other unwanted cells without affecting normal cells. Although the specification suggest to use a conjugate of NTP, the NTP is only released from the composition at the site of a tumor or unwanted cells, it fails to teach how to make and use such NTP conjugates. Moreover, *in vivo* drug delivery in general is unpredictable.

Jain (Scientific American July 1994) discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

*Working examples*

The specification teaches that a method of treating glioma and neuroblastoma cells by AD7C-NTP (SEQ ID NO. 10), where significant cytotoxic effects are observed at 24 hrs and at 96 hours after treatment (see page 43, Example 1). The specification teaches a method of administering AD7C-NTP by direct injection to the skin of normal rats, wherein the necrosis is observed in muscle tissue, subcutaneous connective tissue and dermis at the sites where the AD7C-NTP (SEQ ID NO: 10) was injected (see page

45, Example 2). The specification further teaches a method of treating different human and non-human origin tumors by directly infiltrating the tumor with AD7C-NTP (SEQ ID NO: 10), wherein a significant necrosis of tumor cells after AD7C-NTP infiltration is observed (see page 46, Example 3). However, aside from these data, no working example is provided for a method of treating any conditions by any NTP conjugates. No evidence is provided to one of skill in the art to indicate that any and all NTP conjugates can be used to treat any conditions requiring removal or destruction of cells.

*Guidance in the specification*

The specification fails to teach how to make any NTP conjugates where the activity of NTPs is shut down or inhibited during delivery and turned on only at site of a tumor or unwanted cells. As such, it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

*Level of skill in the art*

The level of skill in the art is high.

*Conclusion*

Thus given the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example of the method of making and/or using the NTP conjugates and no teachings in the prior art balanced only against the high skill level in the art, it is the position of the

examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

### *Claim Rejections - 35 USC § 112, 1st paragraph*

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 17-19, 21, 22, 39-42 and 44-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite "NTP, conjugated, linked, or bound to a protein, a molecule, dendrimers, fullerenes, synthetic molecules, polymers and macromolecules, and antibody-like molecules", "the NTP is part of a single new cloned recombinant molecule consisting of antibody-like binding molecules" and "the NTP composition is cleaved at or near the sites of tumor or other unwanted cells by a tumor- or site-specific enzyme or protease, or by an antibody conjugate that targets tumor or other unwanted cells and so release the NTP". There is a lack of a written description regarding a protein, a molecule, dendrimers, fullerenes, synthetic molecules, polymers, macromolecules, antibody-like molecules" and "tumor- or site-specific enzyme or protease or antibody conjugate". Adequate written description requires more than a

mere statement that it is part of the invention and a reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed protein, molecule, dendrimers, fullerenes, synthetic molecules, polymers, macromolecules, antibody-like molecules, tumor- or site-specific enzyme or protease, and antibody-like binding molecule.

Vas-cath Inc. 1. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, although drawn specifically to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually

defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant claims encompass genus of molecules dendrimers, fullerenes, synthetic molecules, polymers and macromolecules, and antibody-like molecules, and genus of a tumor- or site-specific enzyme or protease, antibody-like binding molecules. The specification provides neither a representative number of molecules, dendrimers, fullerenes, synthetic molecules, polymers and macromolecules, antibody-like molecules, tumor- or site-specific enzymes, proteases and antibody-like binding molecules that encompass the genus nor does it provide a description of structural and functional features that are common to genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant and encompasses molecules or enzymes yet to be discovered, one of skill in the art would reasonably conclude that the applicant is not in possession of the claimed invention.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1 11 1, Friday January 5, 2001.

***Claim Rejections - 35 USC § 112, 1st paragraph, 1st paragraph***

16. Claims 23-29, 31 and 39-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants broadly claim a method of claim 1, wherein said NTP is chosen from the group consisting of AD7C-NTP (SEQ ID NO: 10), the proteins identified by SEQ ID Nos. 2-9, neural pancreatic thread protein, pancreatic thread protein and any fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers thereof. The written description in this instant case only sets forth AD7C-NTP (SEQ ID NO: 10), the proteins identified by SEQ ID Nos. 2-9, art known neural pancreatic thread protein and pancreatic thread protein. There is a lack of a written description regarding the structure and function of the fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID Nos. 2-9, neural pancreatic thread protein and pancreatic thread protein. Therefore the written description is not commensurate in scope with the claims drawn to a method of claim 1, wherein said NTP is chosen from the group consisting of AD7C-NTP (SEQ ID NO: 10), the proteins identified by SEQ ID Nos. 2-9, neural pancreatic thread protein, pancreatic thread protein and any fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers thereof. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential

method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Vas-cath Inc. 1. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, although drawn specifically to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA...'requires

a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). Although the instant specification discloses AD7C-NTP (SEQ ID NO: 10), the proteins identified by SEQ ID Nos. 2-9, the neural pancreatic thread proteins and pancreatic thread proteins that are known in the art, it fails to provide information regarding the structures and biological functions of any fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID Nos. 2-9, the neural pancreatic thread proteins and pancreatic thread proteins. Moreover, the instant claims encompass fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers which may not still have the biological function of neural thread peptides. Therefore, the specification provides neither a representative number of fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID Nos. 2-9, certain neural pancreatic thread proteins and pancreatic thread proteins nor does it provide a description of structural and functional features that are common to the fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID Nos. 2-9, certain neural pancreatic thread proteins and pancreatic thread proteins. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant and encompasses proteins yet to be discovered, the disclosure of the specific species of

genus is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1 11 1, Friday January 5, 2001.

***Double Patenting***

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-7 and 9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7 of U.S. Patent No. 6,924,266B2. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims 1-7 and 9 are drawn a method of treating a condition in a patient requiring removal or destruction of cells comprising administering to a mammal

in need a therapeutically effective amount of a neural thread protein (NTP). Claims are further limited wherein said conditions are a benign or malignant tumor, a hyperplasia, hypertrophy, overgrowth of a tissue and malformation of a tissue.

Claims 4-7 of U.S. Patent NO. 6,924,266B2 are drawn to a method of treating a benign or malignant tumor in a patient comprising local administration of a therapeutically effective amount of a NTP-peptide consisting of SEQ ID Nos: 23-26, 28, 29 and 52.

The specification defines that NTP as neural thread proteins and related molecules as well as fragments, variant, derivative, homolog, reverse-D peptide, and enantiomers of NTP (see specification, pages 9 and 11). Therefore, claims 4-7 of U.S. Patent NO. 6,924,266B2 anticipate instant claims 1-7, and 9 because the instant invention claims a method of treating a genus of condition using a genus of NTP protein, which encompasses a benign or malignant tumor and NTP-peptides as claimed in the U.S. patent No. 6.924,266B2 and the U.S. patent No. 6.924,266B2 claims a method of treating a benign or a malignant tumor using the species of the genus of NTP recited in the instant claims.

***Double Patenting***

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1-7 and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-16 and 18 of copending Application No. 10/294,891 and claims 9-13 and 15 of copending Application No. 10/920,313. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims 1-7 and 9 and their interpretation are set forth above see paragraph 18.

Claims 12-16 and 18 of copending Application No. 10/294,891 are drawn to a method of treating a condition in a patient comprising administration of a therapeutically effective amount of a NTP-peptide consisting of SEQ ID Nos: 8-48. Claims are further limited wherein said conditions are a benign or malignant tumor, a hyperplasia, hypertrophy, overgrowth of a tissue and malformation of a tissue.

Claims 9-13 and 15 of copending Application No. 10/920,313 are drawn to a method of treating a condition in a patient comprising administration of a therapeutically effective amount of a NTP-peptide consisting of SEQ ID No. 8. Claims are further limited wherein said conditions are a benign or malignant tumor, a hyperplasia, hypertrophy, overgrowth of a tissue and malformation of a tissue

The specification defines that NTP as neural thread proteins and related molecules as well as fragments, variant, derivative, homolog, reverse-D peptide, and enantiomers of NTP (see specification, pages 9 and 11). Moreover, claims 12-16 and 18 of copending Application No. 10/294,891 recite "comprising" which is an open language. Therefore, claims 12-16 and 18 of copending Application No. 10/294,891 and claims 9-13 and 15 of copending Application No. 10/920,313 anticipate instant claims 1-7, and 9 because the instant invention claims a method of treating a condition using a genus of NTP protein, which encompasses NTP proteins as claimed in the copending Application Nos. 10/294,891 and 10/920,313 and the copending Application Nos. 10/294,891 and 10/920,313 claims a method of treating a condition using species of the genus of NTP recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hong Sang
Art Unit 1643
Oct. 19, 2005

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER